The LXR agonist T0901317 promotes the reverse cholesterol transport from macrophages by increasing plasma efflux potential

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Abstract The liver X receptors (LXRs) have been shown to affect lipoprotein plasma profile, lipid metabolism, and reverse cholesterol transport (RCT). In the present study, we investigated whether a short-term administration of the synthetic LXR agonist T0901317 (T0) to mice may affect RCT by modulating the capacity of plasma to promote cellular lipid efflux. Consistent with previous data, the pharmacological treatment of mice caused a significant increase of macrophage-derived [^{3}H]cholesterol content in plasma, liver, and feces and resulted in improved capacity of plasma to promote cellular cholesterol release through passive diffusion and scavenger receptor class B type I (SR-BI)-mediated mechanisms. Differently, plasma from treated mice possessed similar or reduced capacity to drive lipid efflux via ABCA1. Consistent with these data, the analysis of plasma HDL fractions revealed that T0 caused the formation of larger, lipid-enriched particles. These results suggest that T0 promotes in vivo RCT from macrophages at least in part by inducing an enrichment of those HDL subclasses that increase plasma capacity to promote cholesterol efflux by passive diffusion and SR-BI-mediated mechanisms.—Zanotti, I., F. Potì, M. Pedrelli, E. Favari, E. Moleri, G. Franceschini, L. Calabresi, and F. Bernini. **The LXR agonist T0901317 promotes the reverse cholesterol transport from macrophages by increasing plasma efflux potential. *J. Lipid Res.* 2008.** 49: **954–960.**

Supplementary key words liver X receptor • high density lipoprotein • passive diffusion • ATP binding cassette A1 • scavenger receptor class B type I

The liver X receptors (LXRs) belong to the family of nuclear hormone receptors that act as transcription factors for several classes of genes (1). The two isoforms, LXRα and LXRβ, differ in distribution and function, the former being highly expressed in liver, intestine, and macrophages, where it is involved in lipid metabolism (2), whereas the latter is ubiquitous and present also in the central nervous system (3).

The role of LXR in atherosclerosis and reverse cholesterol transport (RCT) is no longer in doubt: the induction of genes such as ABC transporters A1 and G1, sterol-regulatory element binding protein-1 (SREBP-1), cholesteryl ester transfer protein, by regulating the absorption of cholesterol in intestine, the conversion of cholesterol in bile acids, lipid efflux, and the synthesis of apolipoproteins, has been shown to protect the arterial wall (4–6).

LXR activation occurs upon the binding of specific agonists with the receptors: this event promotes the formation of a heterodimer with the retinoid X receptor and the binding to promoter sequences on different target genes (2). Natural ligands are represented by oxysterols, such as 22(*R*)-hydroxycholesterol, 20(*S*)-hydroxycholesterol, 27-hydroxycholesterol, and 24,25-epoxycholesterol (7), whereas synthetic compounds have been developed recently. Among them, the nonsteroidal compound T0901317 (T0) has been demonstrated to increase HDL plasma levels (4) and to suppress the development of atherosclerotic lesions (8) in mice. The tertiary amine GW3965 showed protective properties toward the formation of atherosclerotic plaques in mice, not necessarily related to changes in HDL cholesterol concentration (9).

The atheroprotective role of LXR has clearly emerged in studies of genetically modified animals: in mice deficient for both isoforms, aortic lipid deposition is highly increased (10), whereas the deletion of bone marrow LXR in mice increases their susceptibility to atherosclerosis (5). In particular, the expression of LXR in macrophages has

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Abbreviations: cpt-cAMP, 8-(4-chlorophenylthio) cyclic AMP; LXR, liver X receptor; RCT, reverse cholesterol transport; SR-BI, scavenger receptor class B type I; SREBP-1, sterol-regulatory element binding protein-1; T0, T0901317.

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been recognized to be mandatory for the antiatherosclerotic activity (11).

LXR stimulation is also involved in the modulation of the RCT, the process by which excess cholesterol is removed from extrahepatic tissues and transported back to the liver (12). This observation is supported by several lines of evidence: LXR agonists, by upregulating ABCA1 and ABCG1 expression in cell culture, may stimulate cellular cholesterol efflux, the first step of RCT (13, 14). The capacity of LXR to modulate RCT in vivo has been demonstrated directly by Rader's group (15), who showed a stimulated mobilization of cholesterol in different mouse models administered with GW3965. However, despite the large amount of data presented and the convincing data, no explanation for the potential mechanism involved in the LXR effect was provided.

Several works revealed that treatment of mice with T0 or GW3965 induced a significant increase in circulating HDL (4, 8, 16). Because these lipoproteins have a well-established role in cholesterol efflux, representing the physiological lipid acceptor, we wondered whether LXR may promote RCT through the increase in the efflux potential of plasma. To address this question, we treated mice with increasing doses of T0. Once it was confirmed that LXR stimulation in vivo caused the promotion of cholesterol mobilization from macrophages to plasma, liver, and feces, we investigated whether plasma from T0-treated mice possessed a higher capacity to stimulate cholesterol release from cultured cells.

EXPERIMENTAL PROCEDURES

Animals

In the first experiment, 15 week old male BALB/c mice (Charles River, Calco, Italy) were treated by oral gavage with T0 (Alexis Biochemicals, Lausen, Switzerland), 10 mg/kg/day, dissolved in propylene glycol-Tween 80 (4:1) or vehicle only for 8 days. Mice received standard diet and water ad libitum.

In the second experiment, 15 week old male BALB/c mice were treated with T0, 100 mg/kg/day, or vehicle only, as described above.

All experiments were conducted in conformity with the Public Health Service Policy on the Humane Care and Use of Laboratory Animals and performed with the approval of the Ethical Committee for Animal Experiments of the University of Parma.

Measurement of macrophage RCT in vivo

On day 6 of pharmacological treatment, [^{3}H]cholesterol-labeled J774 macrophages prepared as described previously (17) were intraperitoneally injected into mice, which were successively separated into individual cages. On day 8, animals were euthanized and blood and liver were collected. Plasma was separated and counted in a β-counter. Livers were extracted by the Bligh and Dyer method (18) and counted by liquid scintillation addition. Feces were collected at 24 and 48 h after the injection of radiolabeled cells and extracted by the Bligh and Dyer method.

Gene expression analysis by real-time PCR

The isolation of total RNA from liver was achieved using NucleoSpin RNA II according to the manufacturer's instructions (Macherey-Nagel, Duren, Germany). Reverse transcription was done using the cDNA archive kit (Applied Biosystems, Foster City, CA). The resulting cDNA was used for real-time quantitative PCR in the ABI Prism 7000 sequence detection system (Applied Biosystems). The specific primers and TaqMan probes for murine ABCA1 and 18S were obtained from Applied Biosystems (Assays-on-Demand Gene Expression Products and TaqMan Rodent GAPDH Control Reagents). To control for variations in the amount of DNA available for PCR in the different samples, gene expression of the target sequence was normalized in relation to the expression of an endogenous control, 18S.

Evaluation of plasma efflux potential

Mice, treated as described above, were euthanized on day 8; blood was collected from the heart, recovered in plastic tubes, and anticoagulated with 3.8% sodium citrate (one part citrate to nine parts blood). Plasma was isolated by low-speed centrifugation and stored at −80°C until use. Aliquots of plasma were used as acceptors in cholesterol efflux experiments. To study the specific mechanism of lipid efflux, we used different cell types. To characterize scavenger receptor class B type I (SR-BI)-mediated efflux, we tested plasma activity on Fu5AH rat hepatoma cells treated or not with BLT-1, which selectively blocks receptor activity (19), and COS-7 cells, control or transiently transfected with SR-BI. Plasmid cDNA containing SR-BI or plasmid cDNA alone was transiently transfected in this cell line with FuGENE 6 as the carrier using an established procedure (20). Cultures of J774 mouse macrophages incubated in the presence or absence of 0.3 mM 8-(4-chlorophenylthio) cyclic AMP (cpt-cAMP; Sigma) were used as a model for ABCA1-mediated or passive diffusion efflux, respectively. Quantification of cholesterol efflux was performed as described previously (21), using a time zero set of cells to calculate total [^{3}H]cholesterol content in the monolayer. Fractional efflux was calculated as cpm [^{3}H] in the medium/[^{3}H] at time zero × 100.

Measurement of plasma lipids and lipoproteins

Plasma HDL cholesterol levels were determined using a standard enzymatic technique with a Roche Diagnostics Integra 400 autoanalyzer. Lipoproteins were analyzed by gel filtration on a 10/30 Superose 6B column (fast-protein liquid chromatography; Amersham Pharmacia Biotech) at 0.5 ml/min in phosphate-buffered saline containing 0.1 mM EDTA and 0.02% sodium azide. Total cholesterol, phospholipid, and triglyceride concentrations were measured in the collected fractions using standard enzymatic techniques.

Two-dimensional gel electrophoresis

Plasma HDL subclasses were separated by two-dimensional electrophoresis, in which agarose gel electrophoresis was followed by nondenaturing polyacrylamide gradient gel electrophoresis and subsequent immunoblotting (22). In the first dimension, plasma (5 μl) was run on a 0.5% agarose gel; agarose gel strips containing the separated lipoproteins were then transferred to a 3–20% polyacrylamide gradient gel. Separation in the second dimension was performed at 30 mA for 4 h. Fractionated HDLs were then electroblotted onto a nitrocellulose membrane and detected with an anti-apolipoprotein A-I antibody.

Statistical analysis

Results were analyzed by Student's *t*-test with the use of GraphPad Prism software. Efflux data are reported as means of triplicate assays ± SD.

RESULTS

In the first part of this study, we aimed to confirm the impact of LXR stimulation on macrophage-specific RCT in vivo. Different from the previous report (15), we treated animals with the LXR synthetic agonist T0 at 10 or 100 mg/kg/day for 8 days. The former dose was shown to be efficient at reducing atherosclerosis development (8), whereas the latter significantly affected HDL quality and quantity in mice (23).

Indeed, mice that received LXR agonist at both doses showed a higher content of macrophage-derived [^{3}H]cholesterol in plasma (**Fig. 1A, B**). The hepatic content of [^{3}H]cholesterol was higher in mice treated with 100 mg/kg/day T0 than in untreated mice (Fig. 1D), whereas at the lower dose there was no significant difference (Fig. 1C). Importantly, mice treated with T0 excreted significantly more radioactivity in the feces compared with untreated mice (Fig. 1E, F).

As reported previously in the literature, the stimulation of LXR in vivo can affect lipoprotein plasma profile (4, 8, 15, 16) and hepatic gene expression (2). Consistent with these data, in our study we observed an increase in HDL plasma concentration in mice treated with 100 mg/kg/day T0 compared with untreated mice (average ± SD: 110.5 ± 2.1 vs. 41.0 ± 9.9 mg/dl; $P < 0.05$) and a 2.8-fold increase in hepatic *Abca1* mRNA expression, as evaluated by quantitative PCR (data not shown). Because HDLs are the physiological acceptors of cholesterol, we wondered whether the observed increase of RCT, and especially its first step, cholesterol efflux, could be related to a potentiated capacity of plasma to accept cholesterol from cells. Plasma from mice treated with T0 were tested in in vitro cholesterol efflux experiments in different cellular models to specifically verify whether SR-BI, passive diffusion, and/or ABCA1-mediated processes were affected. The first experiment was performed on Fu5AH rat hepatoma cells, which express high levels of SR-BI and have been used exten-

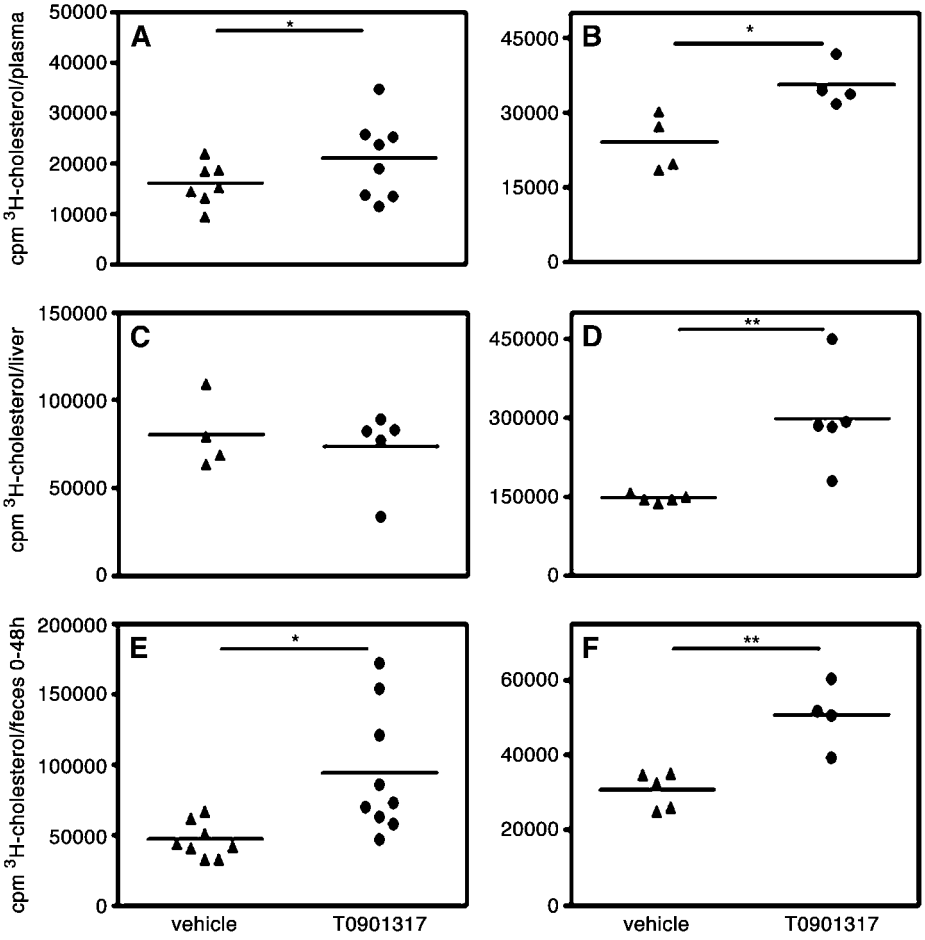

Fig. 1. Liver X receptor (LXR) stimulation impact on macrophage-specific reverse cholesterol transport (RCT) in vivo. Macrophage-derived [^{3}H]cholesterol in plasma (A, B), liver (C, D), and feces (E, F). Aliquots of plasma from vehicle-treated and T0901317 (T0)-treated [10 mg/kg/day (A) or 100 mg/kg/day (B)] mice were counted in a β-counter. Samples of hepatic tissue and feces from vehicle-treated and T0-treated mice [10 mg/kg/day (C, E, respectively) or 100 mg/kg/day (D, F, respectively)] were extracted by the Bligh and Dyer method to isolate the sterol fraction. Quantification of radioactivity content was performed by liquid scintillation counting. Results are expressed as amount of radioactivity in whole plasma, liver, or total feces. * $P < 0.05$, ** $P < 0.01$ versus vehicle-treated mice.

sively to characterize this efflux pathway (22, 24, 25). Here, we demonstrate that treatment of mice with T0 dose-dependently increased cholesterol release to plasma, increasing from 4.7 ± 0.6% in cells exposed to plasma from control mice to 7.4 ± 2.2% ($P < 0.05$) and 9.3 ± 0.2% ($P < 0.001$) in cells exposed to plasma from mice treated with T0 at 10 and 100 mg/kg/day, respectively. To confirm the role of SR-BI in explaining the increased efflux capacity of T0-treated plasma, we repeated the experiment on Fu5AH cells in the presence or absence of BLT-1, which has been demonstrated to selectively and efficiently block SR-BI activity (19). As shown in **Fig. 2** (left panel), although plasma from mice treated with T0 promoted a more efficient release of cholesterol when SR-BI was fully functional, when cells were pretreated with BLT-1 this difference disappeared. To further support the role of this transporter in driving T0-treated plasma efflux capacity, the experiment was repeated in COS-7 cells transfected or not with SR-BI. Whereas in basal conditions plasma from T0-treated mice possessed only a slightly increased efflux potential compared with control plasma, when SR-BI was expressed the difference was significant (Fig. 2, right panel).

The capacity of plasma to drive the efflux that occurs via passive diffusion was evaluated in J774 macrophages. In this system, plasma from T0-treated mice produced an increased efflux over that of control mice (**Fig. 3**); however, upon cell treatment with cpt-cAMP, the increase in T0 plasma acceptor capacity was less pronounced (Fig. 3). Consequently, the contribution of ABCA1 to total efflux, calculated as the difference between the percentage cholesterol efflux from cells upregulated with cpt-cAMP and the percentage cholesterol efflux from control J774 cells, was diminished.

Together, these results suggest that LXR stimulation in vivo may cause the qualitative modifications of plasma lipoprotein profile that altered its efflux potential. Another

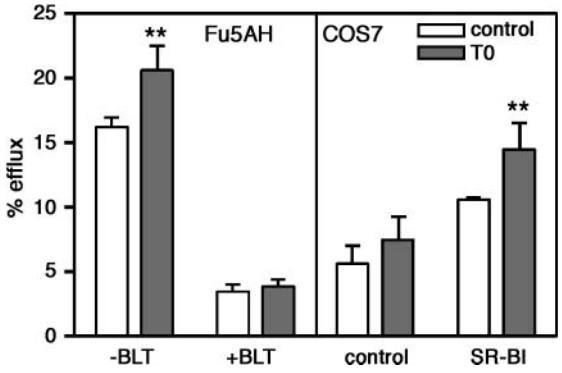

Fig. 2. Efflux potential of plasma from untreated or T0-treated mice: the role of scavenger receptor class B type I (SR-BI). Fu5AH cells, treated or not with BLT-1 (left panel), and COS-7 cells, control or transiently transfected with SR-BI (right panel), were radiolabeled with [^{3}H]cholesterol, equilibrated in an albumin-containing medium, and exposed to 2.5% plasma for 4 h. Efflux was expressed as cpm in medium/cpm at time zero × 100. Values shown are means of triplicate assays ± SD. ** $P < 0.01$ versus Fu5AH cells not treated with BLT-1or versus SR-BI-expressing COS-7 cells exposed to plasma from vehicle-treated mice.

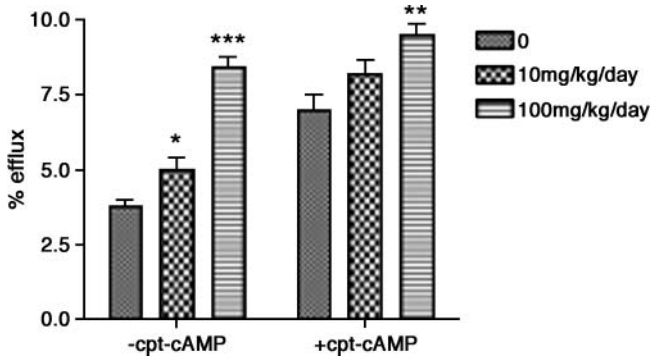

Fig. 3. Efflux potential of plasma from untreated or T0-treated mice: passive diffusion and ABCA1-mediated efflux. J774 cells were radiolabeled with [^{3}H]cholesterol, equilibrated in an albumin-containing medium in the presence or absence of 0.3 mM 8-(4-chlorophenylthio) cyclic AMP (cpt-cAMP), and exposed to 2.5% plasma for 4 h. Efflux was expressed as cpm in medium/cpm at time zero × 100. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ versus cells exposed to plasma from vehicle-treated mice. Error bars represent ± SD.

possibility was that plasma of treated animals could contain sufficient concentrations of drug or an active metabolite to directly stimulate cells to release cholesterol. To rule out this possibility, we performed an experiment with Fu5AH, a cell model in which T0 plasma was more active than in controls, radiolabeling with [^{3}H]cholesterol and exposing to 2.5% plasma from untreated or T0-treated mice for 4 h. Finally, lipid efflux was promoted to normal mouse plasma for 4 h. If plasma from T0-treated mice contained active compounds that directly affected cell efflux capacity, we would expect higher efflux from cells equilibrated in the presence of T0 plasma. On the contrary, in both conditions, we found the same amount of radiolabeled cholesterol in the cell medium (9.1 ± 0.8% vs. 8.9 ± 1.0%; n = 3), suggesting that 4 h of incubation with plasma did not directly affect cell function.

Plasma capacity to stimulate lipid release through a specific mechanism has been shown to depend strictly on the presence of specific particles that act as cholesterol acceptors (26). Therefore, we evaluated the effect of T0 on lipoprotein plasma profile. For this purpose, fast-protein liquid chromatography and two-dimensional gel electrophoresis were carried out on samples of plasma obtained from untreated or T0-treated mice. Cholesterol and phospholipids were higher in all fractions of plasma from animals treated with 100 mg/kg/day T0 (**Fig. 4**), whereas triglycerides were decreased slightly (Fig. 4). Consistent lipid profiles were obtained using the lower dose of drug (10 mg/kg/day) (data not shown).

Two-dimensional gel electrophoresis revealed that HDLs from mice treated with T0 were larger and almost completely lacked the preβ-fraction compared with untreated mice (**Fig. 5**).

DISCUSSION

The antiatherosclerotic role of LXR is supported by several works using either transgenic animals (5, 10) or

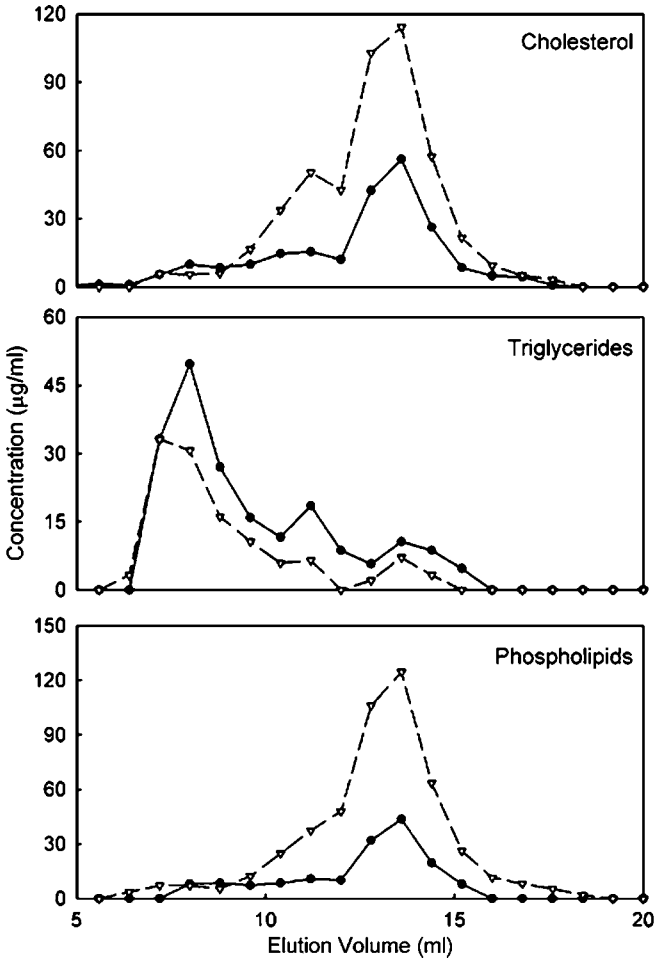

Fig. 4. Elution profiles of untreated (closed circles) and T0-treated (open triangles) mouse plasma by fast-protein liquid chromatography. Mouse plasma (500 μl) was applied on a 30/10 Superose 6B column. The concentrations of cholesterol, triglycerides, and phospholipids in each fraction are indicated on the *y* axis.

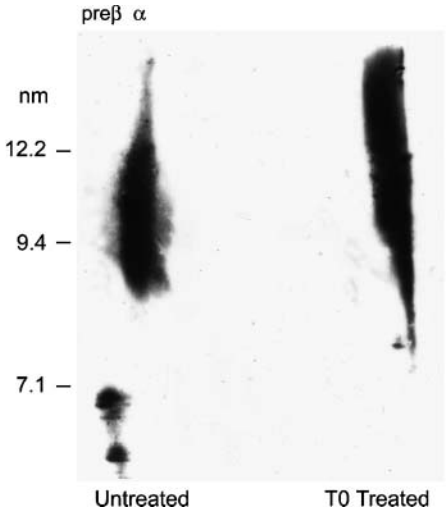

Fig. 5. HDL subclasses in untreated and T0-treated mice. HDL subclasses were separated by two-dimensional electrophoresis and transferred onto a nitrocellulose membrane, on which lipoproteins were detected with an anti-apolipoprotein A-I antibody.

pharmacological activation of these receptors (8, 9). In addition, LXR capacity to promote a well-known antiatherosclerotic process such as the RCT was demonstrated recently in an elegant work (15). The mechanisms by which LXR may exert this beneficial activity are multiple, because several LXR target genes are involved in lipid homeostasis and therefore could provide a positive regulation of lipid metabolism. In particular, the upregulation of ABCA1 and ABCG1, by promoting lipid release from cells, could reasonably account for the reduction of cholesterol accumulation in the atherosclerotic plaque. The promotion of RCT is more difficult to explain, given the complexity of this process, in which several steps and multiple genes are involved. Recently, the concept of macrophagic RCT has emerged (27), indicating the importance of evaluating the specific release of cholesterol from macrophages. This process is of particular relevance because the cholesterol content of macrophages in the vessels is one of the most important determinants of atherosclerosis, and the removal of cholesterol specifically from these cells explains the atheroprotective function of RCT. Thus, finding a method that specifically quantifies the transport of cholesterol from macrophages to liver and feces would allow the potential antiatherosclerotic properties of drugs to be determined.

In this work, we aimed to address the question of a LXR-mediated mechanism of RCT promotion. In the work of Naik et al. (15), despite the large amount of data presented, the authors merely speculated on the mechanism. Consistent with that report, here we reported that the in vivo stimulation of LXR by T0 increased the amount of macrophage-derived cholesterol in plasma and feces in a dose-dependent manner, indicating a stimulation of RCT. The radioactivity content of plasma was higher in mice treated with both doses of T0 compared with untreated mice, suggesting that the first step of RCT, the efflux of cholesterol from peritoneal macrophages, is more efficient upon T0-mediated stimulation of LXR. The analysis of hepatic lipid content showed that treatment with 100 mg/kg/day T0 produced a significant, 2-fold increase in cholesterol amount compared with that in untreated mice. At the lower dose of T0, despite the increase of [^{3}H]cholesterol accumulation in blood and feces, we did not observe a significant increase in the liver. Similar results have been reported by Naik and colleagues (15) with the LXR agonist GW3965; they suggested that at 48 h after the injection of radiolabeled J774 (when animals were euthanized), the excess amount of cholesterol present in the blood after drug treatment could already have been secreted in the feces. Alternatively, the lack of difference in hepatic [^{3}H]cholesterol content may be explained, as proposed by Kruit and colleagues (28), through the existence of an LXR-dependent pathway of fecal sterol output that does not involve the liver. According to this model, upon activation of LXR, plasma-derived cholesterol is eliminated by the intestine independently of biliary secretion. Finally, the final step of RCT was likely to be promoted by an LXR agonist, because at both the early and late time points sterol fecal excretion was increased significantly compared with that in control mice.

The observed increase of [^{3}H]cholesterol in the blood compartment may derive from *1*) an increased capacity of macrophages to release cholesterol or *2*) a potentiated ability of plasma to act as a cellular lipid acceptor. Although a direct effect of T0 on injected J774 efflux capacity cannot be excluded, our data on plasma efflux potential support the second hypothesis.

To verify this, the release of cholesterol from cultured cells exposed to plasma derived from mice treated or not with T0 was measured. SR-BI-mediated cholesterol efflux was promoted more efficiently by T0-treated plasma than untreated plasma. The interaction between plasma and SR-BI was documented using two different cell models: the former was represented by Fu5AH cells, which constitutively express a high amount of the receptor and whose activity can be significantly inhibited by BLT-1 (19); the latter was represented by COS-7 cells, which can be easily and efficiently transfected with SR-BI. In both systems, the ability of T0-treated plasma to selectively promote lipid release through SR-BI was consistent. Efflux that occurs through passive diffusion was evaluated in J774 cells in basal conditions, in which we observed a significant dose-dependent increase of efflux potential from T0-treated plasma. Another cell model, in which no receptors were expressed and efflux could be attributed to a passive diffusion mechanism, was represented by control COS-7 cells; here, T0 plasma capacity to accept cholesterol was only slightly, not significantly, increased compared with controls. This apparent discrepancy could be explained by the use of different cell models, in which a passive diffusion mechanism may differently contribute to total efflux (29). In contrast, T0 plasma presented similar or even reduced efflux potential from ABCA1-expressing cells compared with plasma from untreated mice, as shown by the reduction of ABCA1's contribution to total efflux in cells exposed to T0 plasma. Even if our data for plasma efflux potential proved the increase of passive diffusion and SR-BI-mediated pathways, ABCA1's involvement in vivo cannot be ruled out completely. In fact, it is well known that the typical ABCA1 acceptor is represented by poor lipidated apolipoprotein A-I (22), whose half-life is short. These particles' fate in vivo is either a rapid catabolism by the kidney or the conversion into larger, more stable HDLs upon lipidation via ABCA1 (30). Therefore, we could not exclude the possibility that, in addition to the increased plasma efflux potential, in our model ABCA1 efflux from macrophages also is promoted in vivo, consistent with the expected upregulation of the transporter in these cells.

HDLs represent the physiological acceptors of cholesterol, and the concentration and composition/distribution of these lipoproteins are the main determinants of plasma capacity to promote the release of cholesterol from cells (the so-called efflux potential). In the present work, we report for the first time that the in vivo stimulation of LXR causes a qualitative-quantitative rearrangement of plasma HDL that positively influences the efflux potential of plasma. In agreement with previous works (4, 8, 16), in our study, treatment with the LXR agonist T0 significantly increased HDL levels, possibly via an increased hepatic expression of ABCA1.

As reported in the literature, large, phospholipid-enriched HDLs (α-HDLs) are able to stimulate passive diffusion and SR-BI-mediated efflux (31). Based on efflux data, therefore, we hypothesized that LXR stimulation by T0 could specifically increase the HDL component of plasma able to promote passive diffusion and SR-BI-mediated efflux. This hypothesis was confirmed by fast-protein liquid chromatography and two-dimensional gel electrophoresis analysis, showing that HDLs from mice treated with T0 are larger and enriched with cholesterol and phospholipids. These data are consistent with previous studies reporting that stimulation of LXR in mice resulted in a peculiar enrichment in a population of large HDLs (23, 32). The analysis of HDL subpopulation distribution was also consistent with the lack of increase or even the reduction in lipid efflux to plasma that occurs via ABCA1, as in T0-treated mice the preβ fraction of HDL is strongly reduced.

Therefore, we conclude that stimulation of LXR improves the efflux potential of plasma from treated animals by altering HDL composition and subclass distribution. A direct stimulation of cell efflux capacity by T0 or its metabolites present in the plasma of treated animals is ruled out by the observation that cells pretreated with plasma from T0-treated animals did not show an increased ability to release cholesterol in the cell culture medium compared with plasma from untreated mice.

As reported by many authors (1, 2), LXR stimulation in vivo is responsible for a hypertriglyceridemic state and hepatic steatosis related to the activation of SREBP-1c, stearoyl-CoA desaturase, and fatty acid synthase. Although we did not observe any alteration of triglyceride plasma level, in our study mice that received the T0 showed macroscopic signs of steatosis at both 10 and 100 mg/kg/day. As suggested by others (1), this undesirable side effect, which heavily limits LXR agonist application as a therapeutic agent, could be overcome by the development of LXRβ selective agonists, which keep the positive effect on HDL without affecting fatty acid synthesis.

In conclusion, we confirm the promoting effect of the in vivo stimulation of LXR on macrophages to feces RCT and provide for the first time evidence that this effect is at least in part mediated by the increased efflux potential of plasma.

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